

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-406**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-406

SUPPL #

HFD # 510

Trade Name Fortical Nasal Spray

Generic Name calcitonin-salmon (rDNA origin) nasal spray

Applicant Name Unigene Laboratories, Inc.

Approval Date, If Known August 12, 2005

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

It is a 505(b)(2) application, and the sponsor only had to show that Fortical Nasal Spray is bioequivalent to Miacalcin Nasal Spray.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-313 Miacalcin Nasal Spray

NDA# 17-808 Miacalcin Injection

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND #                      YES                       ! NO   
! Explain:

Investigation #2  
IND #                      YES                       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES                       ! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

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Name of person completing form: Randy Hedin  
Title: Senior Regulatory Management Officer  
Date: August 15, 2005

Name of Office/Division Director signing form: David Orloff  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Randy Hedin  
8/24/2005 01:39:51 PM

David Orloff  
8/24/2005 05:14:13 PM

## PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-406 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: March 6, 2003 Action Date: August 12, 2005

HFD-510 Trade and generic names/dosage form: Fortical [calcitonin-salmon) (rDNAorigin)] Nasal Spray  
Applicant: Unigene Inc. Therapeutic Class: 5S

Indication(s) previously approved: None

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: This new drug application provides for the use of Fortical [calcitonin-salmon) (rDNA origin)] Nasal Spray for the treatment of osteoporosis in women greater than 5 years post menopause with low bone mass relative to healthy premenopausal females.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children  
(The indication is for post menopause women)

There are safety concerns

Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-950/ Terrie Crescenzi  
HFD-960/ Grace Carmouze  
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: None

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337**

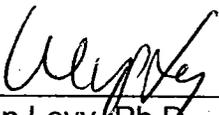
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/s/

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Randy Hedin  
8/16/2005 10:30:58 AM

## DEBARMENT CERTIFICATION STATEMENT

Unigene Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

  
\_\_\_\_\_  
Warren Levy, Ph.D.  
President

7/11/02  
Date

**Section 16 of Fortical Nasal NDA**  
**Debarment Section**

The following people have been checked with the FDA Debarment/  
Disqualification List:

- Employees of Unigene/principals of the company
- TI
- Clinical Investigators and subinvestigators used in N9903/N9904/U1PC-1  
(*Injectable clinical trial which data was incorporated into the PK Section of the NDA*)

*Pamela Schaneen July 26, 2002*

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Pamela Schaneen - Regulatory Affairs Associate  
July 26, 2002

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office) Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34		FROM: HFD-510 Division of Metabolism and Endocrine Drug Products		
DATE July 15, 2005	IND NO.	NDA NO. 21-406	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT September 15, 2004
NAME OF DRUG Fortical (calcitonin-salmon) Nasal Spray		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 3	DESIRED COMPLETION DATE July 30, 2005
NAME OF FIRM Unigene Laboratories, Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW) <input type="checkbox"/> MEETING PLANNED BY				
<b>TRADE NAME REVIEW</b>				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<p>COMMENTS/SPECIAL INSTRUCTIONS: Please review the tradename proposed for Unigene's salmon calcitonin nasal spray. This application is a 505(B)(2) application based on Novartis' Miacalcin Nasal Spray. The firm is proposing the tradename "Fortical Nasal Spray." This is the third follow-up consult request. Your office completed reviews of the tradename on July 31, and December 19, 2003, and March 14, 2004, and found it acceptable if the tradename Fortigel is not approved before this NDA. The user fee goal date is past and [redacted] has indicated it may let us take action on the NDA soon. If you have any questions please contact the project manager.</p> <p>Project Manager - Randy Hedin, 827-6392.  Medical Officer - Theresa Kehoe, 827-6412</p>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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Randy Hedin  
7/15/05 04:38:58 PM



Fortical, be approved. On July 3, 2003, the Fortigel\*\*\* NDA received a 'Not Approved' (NA) action. As of the date of this review, the Fortigel\*\*\* sponsor has not responded to the 'NA' letter. Therefore, the sponsor of Fortigel\*\*\* may still pursue use of this proprietary name at a later date. Thus, DMETS maintains the position that whichever application receives approval first is entitled to the name.

Since the aforementioned reviews, DMETS identified Foradil, an inhalation powder indicated for the maintenance of asthma and COPD, as a potential look-alike drug to Fortical. Foradil and Fortical begin with the letters "For" and have similar orthographic endings ("il" vs. "al"). However, the middle of each name helps to orthographically differentiate between them ("ad" vs. "tic"). Furthermore, the upstroke of the letter "t" appears closer to the beginning of the name Fortical, whereas the upstroke of the letter "d" appears closer to the end of the name Foradil. Both drugs share overlapping storage conditions (refrigerator prior to dispensing and room temperature after dispensing) and may overlap in patient population. However, there are differentiating product characteristics such as strength (2200 international units/mL vs. 12 mcg/inhalation), indication for use (osteoporosis vs. asthma and COPD), dosage form (nasal spray vs. inhalation capsule), route of administration (intranasal vs. oral inhalation), and frequency of administration (QD vs. BID). Although both products may be written without as strength and with "as directed" instructions, the lack of convincing orthographic similarities minimizes the potential for confusion between Foradil and Fortical.

In summary, DMETS has no objections to the use of the proprietary name, Fortical given that Fortigel\*\*\* ( ) is not approved prior to this NDA. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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\*\*\* **NOTE:** This review contains proprietary and confidential information that should not be release to the public.\*\*\*

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/s/

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Felicia Duffy  
3/14/05 03:02:23 PM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
3/14/05 03:14:56 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
3/14/05 03:57:14 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
3/14/05 04:30:16 PM  
DRUG SAFETY OFFICE REVIEWER



NDA 21-406

Unigene Laboratories, Inc.  
Attention: Heike Maaser, Ph.D.  
Director, Regulatory Affairs  
83 Fulton Street  
Boonton, NJ 07005

Dear Dr. Maaser:

We acknowledge receipt on September 16, 2004 of your September 15, 2004 resubmission to your new drug application for Fortical (calcitonin-salmon) Nasal Spray.

We consider this a complete, class 2 response to our December 31, 2003 action letter. Therefore, the user fee goal date is March 16, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any questions, call me at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Randy Hedin, R.Ph.  
Senior Regulatory Management Officer  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Randy Hedin  
9/29/04 10:43:59 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-406

Unigene Laboratories, Inc.  
Attention: Heike Maaser  
Director, Regulatory Affairs  
83 Fulton Street  
Boonton, NJ 07005

Dear Dr. Maaser:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortical (salmon calcitonin) Nasal Spray

We also refer to your April 26, 2004, submission containing a protocol to characterize the human immunogenicity profile of Fortical Nasal Spray.

We have reviewed the referenced material, and you may proceed with the direct ELISA screening for antibody to recombinant salmon calcitonin. However, further information and validation of the in vitro bioassay with CHO-K1 cells is needed prior to implementation of this study.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
7/1/04 05:40:07 PM



NDA 21-406

Unigene Laboratories, Inc.  
Attention: Heike Maaser, Ph.D.  
Director, Regulatory Affairs  
83 Fulton Street  
Boonton, New Jersey 07005

Dear Dr. Maaser:

Please refer to the meeting between representatives of your firm and FDA on February 18, 2004. The purpose of the meeting was to discuss the type of study Unigene is planning to conduct to characterize the human immunogenicity profile of Fortical Nasal Spray.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6392.

Sincerely,

Randy Hedin  
Senior Regulatory Management Officer  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

Meeting Date: February 18, 2004 Time: 1:00 - 1:30 PM Location: Teleconference

NDA 21-406 Fortical (calcitonin salmon) Nasal Spray

Type of Meeting: End-of-review

External participant: Unigene

Meeting Chair: Dr. Theresa Kehoe

External participant lead: Dr. Heike Maaser

Meeting Recorder: Mr. Randy Hedin

Division of Metabolic and Endocrine Drug Products Attendees and titles:

Theresa Kehoe, M.D., Clinical Reviewer  
Randy Hedin, R.Ph., Senior Regulatory Management Officer

External participant Attendees and titles:

Heike Maaser, Ph.D., Director, Regulatory Affairs  
Nozer Mehta, Ph.D., Director Biological Research and Development  
Jim Gilligan, Ph.D., VP Product Development  
Heike Maaser, Director Regulatory Affairs  
Paul Shields, Ph.D. Director of Plant Operations  
Amy Sturmer, Senior Scientist  
James Williams, Regulatory Associate  
Anita Malootian, Clinical Coordinator

Meeting Objectives:

The Meeting was requested by Unigene Laboratories to discuss the study Unigene is planning to conduct to characterize the human immunogenicity profile of Fortical Nasal Spray.

Discussion Points and Decisions (agreements) reached:

- Unigene submitted a background document dated January 21, 2004. The firm requested feedback on its proposal to conduct a human immunogenicity study. The Division stated that the submission did not contain a great deal of information on the proposed study. Overall, the proposal seems adequate. The proposed method of screening for antibodies (direct ELISA) appears adequate. However, a bioassay needs to be developed to further evaluate any antibodies identified (i.e., are the antibodies neutralizing?) and should be included in the protocol. A revised complete

detailed protocol should be submitted to the Division for review and comment before starting the study. The firm thanked us for the advice.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Unigene will submit a revised complete protocol.

Signature, minutes preparer: Randy Hedin March 10, 2004

Concurrence Chair: Theresa Kehoe March 10, 2004

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/s/

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Randy Hedin  
3/12/04 10:52:26 AM



NDA 21-406

Unigene Laboratories, Inc.  
Attention: Heike Maaser, Ph.D.  
Director, Regulatory Affairs  
83 Fulton Street  
Boonton, NJ 07005

Dear Dr. Maaser:

We received your January 21, 2004 correspondence on January 22, 2004 requesting a meeting to discuss your proposal to characterize the human immunogenicity profile of Fortical Nasal Spray. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You did not indicate the type of meeting requested. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C. The meeting is scheduled for:

Date: February 18, 2004  
Time: 1:00 PM  
Location: Teleconference  
CDER participants: Randy Hedin, Senior regulatory Management Officer  
Theresa Kehoe, Medical Officer.

The background information for this meeting was received on January 22, 2004.

If you have any questions, call me at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Randy Hedin  
Senior Regulatory Management Officer  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Randy Hedin  
2/16/04 11:36:06 AM



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/s/

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Yvonne Yang  
12/24/03 09:00:03 AM  
CHEMIST

# Memo

**To:** David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

**From:** Alina R. Mahmud, R.Ph.  
Team Leader, Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420

**Through:** Carol Holquist, R.Ph.  
Deputy Director, Division of Medication Errors and Technical Support  
Office of Drug Safety, HFD-420

**CC:** Randy Hedin  
Project Manager  
HFD-510

**Date:** December 18, 2003

**Re:** ODS Consult 03-0116-1; Fortical (Calcitonin-Salmon) Nasal Spray  
2200 International Units/mL; NDA 21-406.

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In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), DMETS re-reviewed the proposed proprietary name Fortical. Labels and labeling were not provided for review at this time.

Fortical was originally reviewed on May 9, 2003 (see ODS consult 03-0116-1) and was found to have a potential for confusion with Fortigel, a proposed proprietary name by a different manufacturer pending review at the Agency. DMETS had no objections to the name Fortical provided that only one proprietary name, Fortigel or Fortical, be approved. On July 3, 2003, Fortigel was not approved by the Agency. Therefore, DMETS concerns with regard to Fortigel and Fortical were alleviated.

Additionally, since the completion of the Fortical review, DMETS has identified the use of the proprietary name Fortical for an over-the-counter calcium supplement that is being sold via the Internet. The over-the-counter calcium supplement is available as tablets with the directions of use as two tablets twice daily. Additional information about this product may be found on the following website: <http://www.r-downs.com/cgi-bin/output1.pl?request=prod&prod=15>. Although the products are somewhat similar in their effects, DMETS cannot assess the potential for harm if the products are inadvertently dispensed for one another, since the over-the-counter supplement is not regulated by the Agency. Additionally, DMETS has concerns that patients and health practitioners wishing to find additional information on the Internet about the prescription product, Fortical, may encounter information regarding the calcium supplement which may cause confusion. DMETS recommends that the sponsor contact the manufacturer of the over-the-counter calcium supplement to discuss the appropriateness of the proprietary name, Fortical, for the calcium supplement. DMETS does not recommend the use of the same proprietary name for both products as it may cause confusion and error among patients and health practitioners.

In summary, DMETS has no objections to the use of the proprietary name Fortical. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

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Alina Mahmud  
12/19/03 09:17:50 AM  
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips  
12/19/03 09:36:50 AM  
DRUG SAFETY OFFICE REVIEWER



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** December 2, 2003

<b>To:</b> Heike Maaser	<b>From:</b> Randy Hedin
<b>Company:</b> Unigene Laboratories, Inc.	Division of Division of Metabolic and Endocrine Drug Products
<b>Fax number:</b> 973-331-9376	<b>Fax number:</b> 301-443-9282
<b>Phone number:</b> 973-402-9337	<b>Phone number:</b> (301) 827-6392
<b>Subject:</b> Discipline Review Completed for NDA 21-406 Microbiology Comments	

**Total no. of pages including cover:** 2

**Comments:**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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**Document to be mailed:**      • YES       NO

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**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.

Dear Dr. Maaser:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortical (salmon calcitonin) Nasal Spray.

Our review of the microbiology section of your submissions is complete, and we have identified the following deficiencies:

1. It is recommended that acceptance criteria for environmental samples, including in-process pharmaceutical water, be described as alert and action levels (not limits), which is consistent with USP <1231>. The term "limits" is not recommended (per USP <1231>).
2. Numerical values for alert and action levels for Total Microbial Count and for Total Yeast and Mold Count are acceptable. However, the numerical acceptance criteria for \_\_\_\_\_ ) are not acceptable (provided on page 16 of the CMC section 4.3.5.2). Pharmaceutical water systems should not contain \_\_\_\_\_ (Michaels, D.L. "Validation and control of deionized water systems," Letter to the drug industry from Acting Associate Director for Compliance, Bureau of Drugs, FDA. August 1981). Detection of \_\_\_\_\_ should result in investigation and corrective action.
3. Referring to microbiological data for water from point of use sampling ports (provided on page 16 of the CMC section 4.3.5.2), the test method for \_\_\_\_\_ is described by reference to USP <1231>, but that section of USP has no test for \_\_\_\_\_. A test method should accompany the acceptance criterion. Please include a minimum volume for the sample tested.
4. Please confirm the method used for the Total Aerobic Microbial Count of Purified Water by providing a summary of the methods or a standard operating procedure (SOP).

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

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/s/

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Randy Hedin  
12/2/03 09:41:37 AM  
CSO

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

**DATE RECEIVED:** 03/27/03

**DUE DATE:** 05/26/03

**ODS CONSULT #:** 03-0116

**TO:** David G. Orloff, M.D.  
Director, Division of Metabolism and Endocrine Drug Products  
HFD-510

**THROUGH:** Durand M. Hedin  
Project Manager  
HFD-510

**PRODUCT NAME:**  
**Fortical** (Calcitonin-Salmon) Nasal Spray  
2200 International Units/mL

**NDA SPONSOR:** Unigene Laboratories, Inc.

**NDA #:** 21-406

**SAFETY EVALUATOR:** Jinhee L. Jahng, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Metabolism and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Fortical" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proposed proprietary name Fortical provided that **only one name**, Fortical (NDA 21-406) or Fortigel ( ~~Fortigel~~ ), is approved. The acceptability of the proposed proprietary name Fortical depends on which application, Fortical or Fortigel, receives approval first, as these two names may not coexist due to their similarities. The review division for Fortigel has been informed via telephone of this determination.

This is considered a tentative decision. This name and its associated labels and labeling must be reevaluated 90 days prior to the expected approval. A re-review of the name before NDA approval will rule out any objections based upon approvals of the other proprietary/established names from this date forward.

2. DMETS recommends the labeling revisions as outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the name Fortical acceptable from a promotional perspective.

Carol Holquist, R.Ph.  
Deputy Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 9, 2003  
NDA #: 21-406  
NAME OF DRUG: Fortical (Calcitonin-Salmon) Nasal Spray  
2200 International Units/mL  
NDA HOLDER: Unigene Laboratories, Inc.

**\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\***

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Metabolism and Endocrine Drug Products (HFD-510), for assessment of the proprietary name "Fortical", regarding potential name confusion with other proprietary or established drug names. The container label, carton and insert labeling were provided for review.

PRODUCT INFORMATION

Fortical (Calcitonin-Salmon) Nasal Spray is a polypeptide hormone which inhibits bone resorption by direct action on osteoclasts. It is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause with low bone mass relative to healthy premenopausal women. The recommended dose of Fortical is one spray (200 International Units) per day administered intranasally, alternating nostrils daily. Each 3.5 mL bottle contains enough medication for 28 doses.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to "Fortical" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic

<sup>1</sup> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/database within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

search system (TESS) was conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Fortical. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Fortical. Similarly, through independent review, two additional drug names (Florical, Fortamet<sup>\*\*\*</sup>) were also determined to have potential for confusion with the proposed names. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage.
2. DDMAC did not have concerns with Fortical in regard to promotional claims:

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<sup>4</sup>WWW location <http://www.uspto.gov/main/trademarks.htm>

<sup>5</sup>Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com).

<sup>\*\*\*</sup> Pending approval proprietary and confidential information that should not be released to the public.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Fortical	Calcitonin-Salmon Nasal Spray 2200 International Units/mL	One spray (200 International Units) intranasally per day, alternating nostrils daily.	
Fiorinal	Aspirin/Butalbital/Caffeine Capsules 325 mg/50 mg/40 mg Aspirin/Butalbital/Caffeine Tablets 325 mg/50 mg/40 mg	1 – 2 tablets/capsules every 4 hours as needed.	SA
Fioricet	Acetaminophen/Butalbital/Caffeine Tablets 325 mg/50 mg/40 mg	1 – 2 tablets/capsules every 4 hours as needed.	LA
Fortamet***	Metformin-Extended Release Tablets 500 mg, 1000 mg	1000 mg once daily with the evening meal.	LA
Xenical	Orlistat Capsule 120 mg	1 capsule three times daily with meals.	LA
Florical	Sodium Fluoride/Calcium Carbonate Capsules 3.75 mg/145 mg Sodium Fluoride/Calcium Carbonate Tablets 3.75 mg/145 mg	1 capsule/tablet daily.	SA/LA
<del>Fortigel</del>	<del>_____</del>	<del>_____</del>	

\*Frequently used, not all-inclusive  
 \*\*LA (look-alike), SA (sound-alike)  
 \*\*\*Pending approval proprietary and confidential information that should not be released to the public.

**B. PRESCRIPTION ANALYSIS STUDIES**

**1. Methodology:**

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Fortical with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Fortical (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

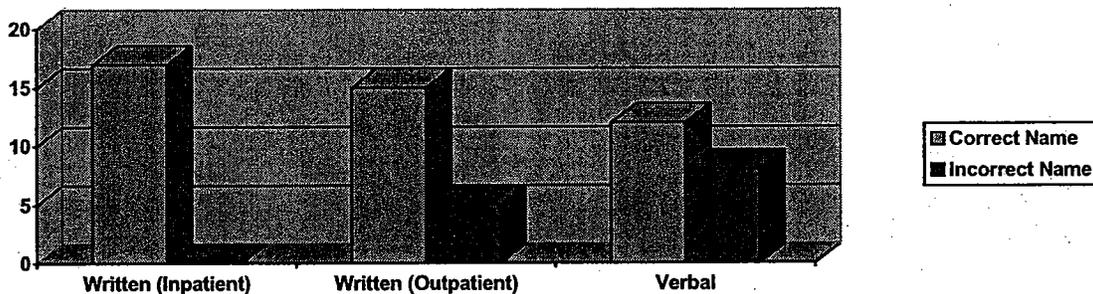
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p><i>Fortical #1</i></p> <p><i>1 spray qd intranasally</i></p>	<p>Fortical 1 spray qd intranasally, alternating nostrils daily. No refills.</p>
<p>Inpatient RX:</p> <p><i>Fortical 1 spray qd intranasally</i></p>	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	17 (44%)	17 (100%)	0 (0%)
Written Outpatient	31	20 (64%)	15 (75%)	5 (25%)
Verbal	35	20 (57%)	12 (60%)	8 (40%)
Total	105	57 (54%)	44 (77%)	13 (23%)



Among the written inpatient prescriptions, 17 of 17 (100%) participants interpreted the name correctly.

In the written outpatient prescriptions, 5 of 20 (25%) participants interpreted the name incorrectly. Some of the incorrect interpretations from the prescriptions included Forticed (2 occurrences), Fortizel, Forticol, and Forticel. None of the interpretations are similar to a currently marketed drug product.

Among the verbal prescription study participants for Fortical, 8 of 20 (40%) participants interpreted the name incorrectly. Of the correct interpretations, two variations were provided, FortiCal (2 occurrences) and Forti-Cal. Many of the incorrect name interpretations were misspelled/phonetic variations of "Fortical". Some of the incorrect interpretations included Fortacal (2 occurrences), Fordical, Fortecal (4 occurrences), and ForteCal. None of the interpretations are similar to a currently marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

**\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\***

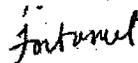
In reviewing the proprietary name, Fortical, the primary concerns related to look-alike, sound-alike confusion with names already in the U.S. marketplace, Fortigel<sup>\*\*\*</sup>, Fiorinal, Xenical, and Fioricet. However, Fiorinal and Fioricet were determined not to have potential sound-alike or look-alike confusion due to the significant differences in their prefixes and suffixes. Similarly, through independent review, two additional drug names (Florical and Fortamet<sup>\*\*\*</sup>) were also determined to have potential for confusion with the proposed names. The products having the greatest potential for name confusion with Fortical were Florical, Xenical, and two unapproved drug names (Fortigel<sup>\*\*\*</sup> and Fortamet<sup>\*\*\*</sup>) still under review in the Agency.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Fortical could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

1. Fortamet<sup>\*\*\*</sup> and Fortical have potential for look-alike confusion. Fortamet is an antidiabetic agent which will be available as a 500 mg and 1000 mg tablet. Both names have three syllables, eight letters, and share the prefix "Fort". However, the "met" in Fortamet and "cal" in Fortical are distinguishable (see writing sample below), even if the second "t" in Fortamet is not crossed prominently. In addition, Fortamet is an oral agent available in two different strengths while Fortical is intranasally administered and available in one, non-overlapping strength. Fortamet and Fortical differ in route of administration (oral vs. nasal), dosage strength (two vs. one), and indication for use, but share the same dosing schedule (once daily). Though Fortamet and Fortical have the potential for look-alike confusion, the likelihood for confusion is minimized because of the differences mentioned above.



Fortical



Fortamet

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\*\*\* This review contains proprietary and confidential information that should not be released to the public.

2. Xenical and Fortical have potential for look-alike confusion. Xenical is a non-systemic inhibitor of gastrointestinal lipases indicated for obesity management. Xenical and Fortical both end with "ical" and despite the differences in prefixes, the "X" and "F" when scripted have the potential to look-alike, increasing the likelihood for look-alike confusion (see writing sample below). However, the products are distinguishable because of differences in appearance when comparing the "ort" (Fortical) vs. "eni" (Xenical) segment of the name.



Fortical



Xenical

Although Fortical and Xenical are available in one strength, lack of convincing look-alike potential and differences in dosage schedules (once daily vs. three times daily), indications, routes of administration, and dosage form minimize the potential for confusion.

3. Florical and Fortical have potential for sound-alike and look-alike confusion. Florical is a calcium and fluoride supplement. Florical and Fortical both have three syllables and contain eight letters, of which they share seven. The prominent sound of "F" and "or" in "Flor/For" increase the likelihood that the two names could inadvertently be mistaken for the other. Likewise, the identical suffix "ical" increases this likelihood for confusion. The only variance in spelling is in Florical's "l" and Fortical's "t" (see writing sample below). Despite these similarities, data from IMS Health<sup>5</sup> indicates that sales usage during calendar months December 2002 – May 2003 is low. Additionally, Florical is an over-the-counter (OTC) dietary supplement whereas Fortical is dispensed by prescription (Rx) only. The products also differ in dosage form and route of administration. Given that usage of Florical is low, in addition to the other dissimilarities, there is insufficient evidence at this time to conclude that the proposed drug would be confused with Florical.



Fortical

Fortical

Florical

Florical

<sup>5</sup> Data provided by IMS HEALTH, National Sales Perspective™ Combined Data from Retail and Non-Retail, On-line.

1   Page(s) Withheld

  X   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

*Withheld Track Number: Administrative-\_\_\_\_\_*

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Fortical, DMETS focused on safety issues relating to possible medication errors. We have identified the following areas of possible improvement which might minimize potential user error.

#### A. CONTAINER LABEL

1. The use of the abbreviation "IU" in conjunction with a product strength is dangerous. It has been misinterpreted to mean intravenous. Revise "IU" to read "International Units".
2. Increase the contrast between the blue background and the black font color of the established name to improve readability.
3. Relocate "200 International Units/dose" closer to the established name.
4. Relocate "For Intranasal Use Only" to the primary display panel.

#### B. CARTON LABELING

1. See comment under A1 and A3.
2. Change package content information from "1 x 3.5 mL fill bottle and 1 spray applicator" to "Each carton contains: 1 x 3.5 mL fill bottle and 1 spray applicator".
3. Increase prominence of "Important patient information for activation of pump is enclosed". i.e. move comment to beginning of Dose recommendation section, use bold type, and/or contrasting color.
4. Use consistent instructions for administration in the package insert and carton labeling. Change "One spray per day administered intranasally" to "One spray per day administered intranasally, alternating nostrils daily."

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#### IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary name Fortical provided that **only one name**, Fortical (NDA 21-406) **or** Fortigel ( ), is approved. The acceptability of the proposed proprietary name Fortical depends on which application, Fortical or Fortigel, receives approval first, as these two names may not coexist due to their similarities. The review Division for Fortigel has been informed vial telephone of this determination.

This is considered a tentative decision. This name and its associated labels and labeling must be reevaluated 90 days prior to the expected approval. A re-review of the name before NDA approval will rule out any objections based upon approvals of the other proprietary/established names from this date forward.

2. DMETS recommends the labeling revisions as outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
3. DDMAC finds the proprietary name Fortical acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

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Jinhee L. Jahng, Pharm.D.  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

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Alina Mahmud, R.Ph.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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/s/

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Jinhee Jahng  
7/31/03 09:47:45 AM  
PHARMACIST

Alina Mahmud  
7/31/03 01:15:16 PM  
PHARMACIST

Carol Holquist  
7/31/03 01:45:53 PM  
PHARMACIST

Jerry Phillips  
7/31/03 02:14:47 PM  
DIRECTOR



NDA 21-406

Unigene Laboratories, Inc,  
Attention: Heike Maaser, Ph.D.  
Director of Regulatory Affairs  
83 Fulton Street  
Boonton, NJ 07005

Dear Dr. Maaser:

Please refer to your March 5, 2003 new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortical (calcitonin-salmon) Nasal Spray.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on May 4, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
5/7/03 06:35:51 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-406

Unigene Laboratories, Inc.  
Attn: Ronald S. Levy, Ph.D.  
Executive Vice President  
110 Little Falls Road  
Fairfield, NJ 07004

Dear Dr. Levy:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fortical<sup>®</sup> (calcitonin-salmon) Nasal Spray  
Review Priority Classification: Standard (S)  
Date of Application: March 5, 2003  
Date of Receipt: March 5, 2003  
Our Reference Number: NDA 21-406

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 4, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 5, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic & Endocrine Drug Products, HFD-510  
Attention: Fishers Document Room, 8B45  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-406

Page 2

If you have any questions, call me at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Randy Hedin, R.Ph.  
Senior Regulatory Management Officer  
Division of Metabolic & Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Randy Hedin  
3/25/03 09:39:21 AM

SEP 10 2002

Food and Drug Administration  
Rockville MD 20857

Pamela Schaneen  
Regulatory Affairs Associate  
Unigene Laboratories, Inc.  
110 Little Falls Road  
Fairfield, NJ 07004

**RE: Unigene Laboratories – Request for Extension of Small Business Waiver,  
Waiver Request # 2003.001**

Dear Ms. Schaneen:

This responds to your June 10, 2002, letter requesting an extension of the small business waiver granted September 28, 2001, for the human drug application fee for the new drug application (NDA) for Fortical Nasal Spray. This waiver was originally granted under the small business waiver provision of section 736(d)(1)(E)<sup>1</sup> of the Federal Food, Drug, and Cosmetic Act (the Act). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Unigene Laboratories, Inc. (Unigene), for an extension of the waiver.

According to your waiver extension request, Unigene is a small business having fewer than five hundred employees worldwide. You recently entered a partnership with GlaxoSmithKline (GSK) for a different program involving another compound, but you note that GSK does not own any Unigene securities. Unigene expects to file the NDA for Fortical Nasal Spray (NDA 21-406) in the fourth quarter of 2002. This will be your first drug application in the United States.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate<sup>2</sup> submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets the following criteria: (1) a business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Unigene's request for extension of the small business waiver for Fortical Nasal Spray (NDA 21-406) is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated August 23, 2002, that Unigene has fewer than 500 employees, and that Unigene has no affiliates. Second, according to FDA

<sup>1</sup> 21 U.S.C. 379h(d)(1)(E).

<sup>2</sup> "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

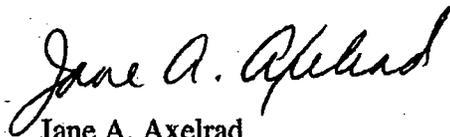
records, the marketing application for Fortical Nasal Spray will be the first human drug application, within the meaning of the Act, to be submitted to FDA by Unigene. Consequently, your request that the small business waiver of the application fee for Fortical Nasal Spray be extended is granted, provided that FDA receives the marketing application for Fortical Nasal Spray no later than August 23, 2003, 1 year after the effective date of the size determination made by SBA. This decision effectively cancels the original small business waiver for the application fee for NDA 21-406 (Waiver Request 2003.001).

FDA records show that Unigene's NDA 21-406 has not yet been submitted to FDA. Please include a copy of this letter with your application when it is submitted. If FDA refuses to file the application or Unigene withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Unigene should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,



Jane A. Axelrad  
Associate Director for Policy  
Center for Drug Evaluation and Research

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# USER FEE COVER SHEET

## See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS  <i>Unigene Laboratories, Inc. 110 Little Falls Road Fairfield, NJ 07004</i>		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  <i>NDA #21 - 406</i>				
2. TELEPHONE NUMBER (Include Area Code)  <i>( 973 ) 882-0860</i>		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA).				
3. PRODUCT NAME  <i>Fortical Nasal Spray (recombinant calcitonin-salmon)</i>		6. USER FEE I.D. NUMBER <i>N/A</i> <i>User Fee Waiver Granted</i>				
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.  <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)  <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)  <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)  <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)  <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)						
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO (See Item 8, reverse side if answered YES)						
<p>Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table><tr><td>Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td><td>Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</td><td>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</td></tr></table>				Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.				
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  <i>Warren P. Levy, Ph.D. Waddy</i>		TITLE  <i>President</i>	DATE  <i>September 24, 2002</i>			

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

### Application Information

NDA 21-406	Efficacy Supplement Type SE-	Supplement Number
Drug: Fortical (calcitonin salmon) Nasal Spray		Applicant: Unigen Laboratories
RPM: Randy Hedin		HFD-510 <span style="float: right;">Phone # 301-827-6392</span>
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 20-313 Miacalcin Nasal Spray
<b>❖ Application Classifications:</b>		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		Rx
<b>❖ User Fee Goal Dates</b>		
		March 16, 2005
<b>❖ Special programs (indicate all that apply)</b>		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input checked="" type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
<b>❖ Application Integrity Policy (AIP)</b>		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
<b>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</b>		
		<input checked="" type="checkbox"/> Verified
<b>❖ Patent</b>		
• Information: Verify that form FDA-3542a was submitted.		<input type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input checked="" type="checkbox"/> IV

	21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
<ul style="list-style-type: none"> <li>For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).</li> </ul>	( X ) Verified
❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> </ul>	
<ul style="list-style-type: none"> <li>Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</li> </ul>	( ) Yes, Application # _____ ( X ) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	May 5, 2003
<b>General Information</b>	
❖ Actions	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	( X ) AP ( ) TA ( ) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	AE December 31, 2003
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	( X ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	( ) Yes ( X ) Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	( X ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	March 11, 2005
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	March 5, 2003
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	DMETS July 31 & December 19, 2003
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>Applicant proposed</li> </ul>	March 11, 2005
<ul style="list-style-type: none"> <li>Reviews</li> </ul>	

❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	June 12, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	None
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) ( <i>indicate date for each review</i> )	Medical Team Leader December 31, 2003 Division Director Memo August 5, 2005
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	December 30, 2003 June 14, 2004 April 13, 2005
❖ Microbiology (efficacy) review(s) ( <i>indicate date for each review</i> )	None
❖ Safety Update review(s) ( <i>indicate date or location if incorporated in another review</i> )	None
❖ Risk Management Plan review(s) ( <i>indicate date/location if incorporated in another rev</i> )	None
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	None
❖ Demographic Worksheet ( <i>NME approvals only</i> )	NA
❖ Statistical review(s) ( <i>indicate date for each review</i> )	January 5, 2004
❖ Biopharmaceutical review(s) ( <i>indicate date for each review</i> )	December 17, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date for each review</i> )	None
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None
• Bioequivalence studies	None
<b>CMC Information</b>	
❖ CMC review(s) ( <i>indicate date for each review</i> )	December 24, 2003 February 10, 2004

	June 2, 2004 August 5, 2004 February 11, 2005
❖ Environmental Assessment	
• Categorical Exclusion ( <i>indicate review date</i> )	December 24, 2003
• Review & FONSI ( <i>indicate date of review</i> )	
• Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Microbiology (validation of sterilization & product sterility) review(s) ( <i>indicate date for each review</i> )	November 21, 2003 November 9, 2004
❖ Facilities inspection (provide EER report)	Date completed: September 30, 2004 ( X ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( X ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	December 5, 2003 February 1, 2005
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	None
❖ CAC/ECAC report	None

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/s/

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Randy Hedin  
12/31/03 12:46:05 PM